

EXHIBIT AA

Handbook of Pharmaceutical Analysis

edited by

Lena Ohannesian

*Mcneil Consumer Healthcare Company
Fort Washington, Pennsylvania*

Antony J. Streeter

*The R. W. Johnson Pharmaceutical Research Institute
Spring House, Pennsylvania*



MARCEL DEKKER, INC.

NEW YORK • BASEL

ISBN: 0-8247-0462-2

This book is printed on acid-free paper.

Headquarters

Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution

Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 41-61-261-8482; fax: 41-61-261-8896

World Wide Web

<http://www.dekker.com>

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Current printing (last digit):

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Table 6 Crystal Forms of Nedocromil

| Salt form | Crystal forms | Ref. |
|-----------|------------------|------|
| Free acid | Unsolvated | 31 |
| Calcium | Pentahydrate | 34 |
| | 8/3 Hydrate | |
| Magnesium | Pentahydrate | 32 |
| | Heptahydrate | |
| | Decahydrate | |
| Sodium | Trihydrate | 35 |
| | Heptahemihydrate | |
| Zinc | Pentahydrate A | 33 |
| | Pentahydrate B | |
| | Heptahydrate | |
| | Octahydrate | |

IV. SOLID FORM SELECTION

It is obvious from the preceding discussion that salt and solid form selection are intertwined. The propensity of a compound, either neutral or a salt, to exist in different crystal forms is considered as part of the salt selection process. However, once selected for inclusion in drug product, the solid-state properties of a given compound must be evaluated in detail. The following section describes the solid-form selection process as it is carried out with a single chemical entity.

A. Solid Forms

The solid forms attained by organic compounds span a range of molecular order (Fig. 21). At one extreme is the amorphous state, characterized by no regular arrangement of molecules, as in a liquid. At the other is the crystalline state. In a crystal the molecules exist in fixed conformations and are packed against each other in a regular way. However, there are few if any "perfect" crystals. Imperfections in the packing arrangement during growth of a crystal can occur in many ways and, when present in sufficient number, provide a poor-quality crystal. Introduce enough packing dislocations to disrupt every intermolecular interaction, and the amorphous state results. Between amorphous and crystalline forms there can be states of partial order, as in liquid crystals.

Generally, organic molecules prefer to exist in crystalline form when solid. Amorphous material, even when isolable, is thermodynamically less stable than crystalline material. The practical consequence of this is that there is energetic

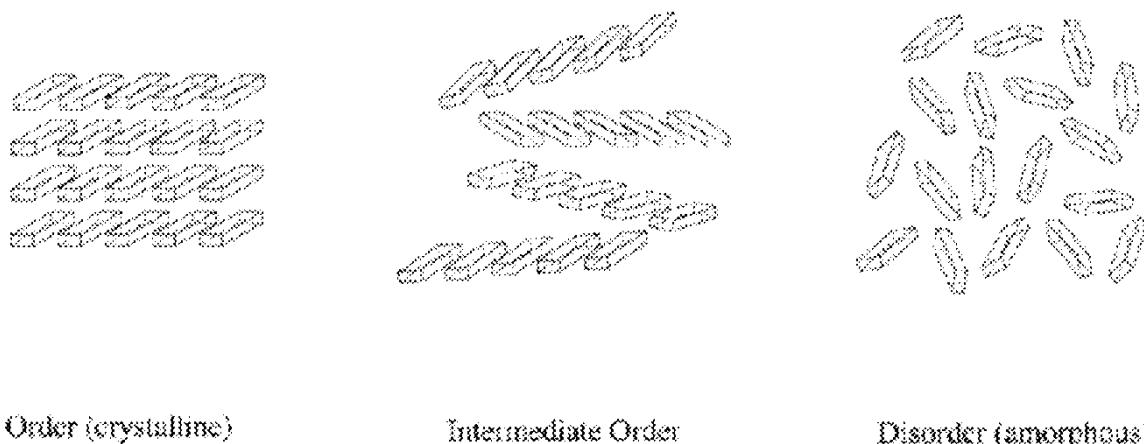


Fig. 21 An illustration of the concept of molecular order in solids.

pressure for an amorphous solid to crystallize, so selection of an amorphous form of a drug for development must be made with this in mind.

In addition to variations in the relative amount of molecular order in solids, there can also be variations in the nature of the order. Different crystalline arrangements of the same molecule can exist; this phenomenon is known as polymorphism. All types of substances exhibit this behavior, including elements, inorganic compounds, and organic compounds. Different crystal forms of elements are called allotropes, while different crystal forms of inorganic or organic compounds are called polymorphs. The propensity for polymorphism in organic compounds is great. In a crystalline organic solid, the forces holding the crystal together, the intermolecular bonds, are much weaker than those holding each molecule together, the intramolecular bonds. Typical intermolecular attractions consist of van der Waals and hydrogen bonds, which range in energy from <0.1 to 8 kcal/mole. Intramolecular covalent bonds range from about 50 to 200 kcal/mole. Thus, only small energy changes need be associated with changes in packing arrangements.

In many cases organic compounds incorporate water or solvents into their crystal lattice. These species are called hydrates or solvates, respectively. Crystals of this type are not strictly polymorphic, which is, by definition, different crystalline arrangements of a single substance. Practically, however, hydrates and solvates exhibit the same range of property differences as do polymorphs and must be considered as viable candidates in the form selection process.

In hydrates and solvates, the amount of water or solvent incorporation can vary. Often, stoichiometric amounts are found, but not always at a 1:1 ratio of water (solvent) to organic molecule. Some common hydrate ratios are shown in Table 7. Many compounds form hydrates or solvates, and examples are given